RISK FOR INCIDENT OA BY EFFUSION SYNOVITIS AND HOFFA SYNOVITIS					
		Overall N (%)	Cases N (%)	Controls N (%)	Hazard ratio (95% CI)
BASELINE FOR EFFUSION-SYNOVITIS (N=126)	Effusion-synovitis present	17 (13.5)	13 (20.6)	4 (6.4)	5.5 (1.2–24.8)
	Effusion-synovitis Absent	109 (86.5)	50 (79.4)	59 (93.7)	
BASELINE FOR HOFFA SYNOVITIS (N=125)	Hoffa synovitis present	39 (31.2)	24 (38.7)	15 (23.8)	2 (0.9–4.5)
	Hoffa synovitis absent	86 (68.8)	38 (61.3)	48 (76.2)	
P1 FOR EFFUSION-SYNOVITIS (N=118)	Effusion-synovitis present	28 (23.7)	24(40.7)	4 (6.8)	7.7 (2.3–25.5)
	Effusion-synovitis Absent	90 (76.3)	35 (59.3)	55 (93.2)	
P1 FOR HOFFA SYNOVITIS (N=117)	Hoffa synovitis present	42 (35.9)	27 (46.6)	15 (25.4)	3 (1.2–7.6)
	Hoffa synovitis absent	75 (64.1)	31 (53.5)	44 (25.4)	
P0 FOR EFFUSION- SYNOVITIS (N=118)	Effusion-synovitis present	45 (38.1)	36 (61.0)	9 (15.3)	28 (3.8–205.8)
	Effusion-synovitis Absent	73 (61.9)	23 (39.0)	50 (84.8)	
P0 FOR HOFFA SYNOVITIS (N=116)	Hoffa synovitis present	43 (37.1)	29 (50)	14 (24.1)	4 (1.5–10.7)
	Hoffa synovitis absent	73 (62.9)	29(50)	44 (75.9)	

67
DIRECT IN VIVO EVIDENCE OF ACTIVATED MACROPHAGES IN HUMAN OSTEOARTHRITIS

V. Byers Kraus [†], G. McDaniel [†], J.L. Huebner [†], T. Stabler [†], C. Pieper [†], R.E. Coleman [†], N.A. Petry [†], P.S. Low [‡], J. Shen [‡], P. Mitchell [§]. [†] *Duke Univ., Durham, NC, USA;* [‡] *Purdue Univ., West Lafayette, IN, USA;* [§] *Eli Lilly, Indianapolis, IN, USA*

Purpose: Although it is well accepted that activated synovial macrophages play a key role in Rheumatoid Arthritis, the role of inflammation in Osteoarthritis (OA) is controversial. The purpose of this study was to investigate the involvement of activated macrophages in OA through a new imaging modality called FolateScan imaging.
Methods: FolateScan (Endocyte, West Lafayette, Indiana) is a scintigraphic imaging technique that provides a method of detecting activated but not resting monocytes or macrophages. The radioligand for this imaging technology, Etarfolatide (or EC20), consists of a targeting moiety (folic acid) linked to a chelating moiety enabling coupling to technetium-99m (99mTc). Targeting to activated macrophages is achieved through binding of folate receptor β on the surface of activated macrophages. A total of 25 participants (both knees studied) with symptomatic radiographic knee OA of at least one knee were recruited for the study. Single photon emission computed tomography with computed tomography coregistration (SPECT/CT) of each knee was performed to precisely localize radioligand uptake with regard to anatomical structures of the knee; the intensity of uptake was scored by an experienced reader (REC) on a 0-3 scale for the synovium, joint capsule, and subchondral bone in all three compartments of the knee. Whole body scintigraphy was also performed to identify other sites of 99mTc-EC20 uptake for correlation with joint symptoms. We evaluated the associations of intensity of 99mTc-EC20 uptake with radiographic OA severity including joint space narrowing (JSN) and osteophyte (OST) scored with the aid of a standard radiographic atlas, and severity of joint symptoms (pain, aching, stiffness); we fit models using generalized estimating equations with control for age, gender and body mass index (BMI). P values <0.05 were considered significant.
Results: The cohort was 72% female, 92% Caucasian, mean (SD) age 62.4+15.8 years (range 30-89), and mean (SD) body mass index (BMI) 29.2+4.8 (range 22.5-38.4) kg/m2. By Kellgren Lawrence grading, all knees showed some evidence of radiographic OA spanning the full range of severities with KL1 (24%), KL2 (26%), KL3 (32%), KL4 (18%). Intra-rater reliability of FolateScan scoring was high (k statistic range 0.68-0.90). There was only one adverse event during the study; one participant reported temporary mild dysgeusia. The presence of activated macrophages was detected in the majority (66%) of knees (n=50); 28% of knees had activated macrophages in more than one knee compartment. Synovial and joint capsular macrophages were both strongly associated with joint space narrowing, osteophyte severity, and knee symptoms (see Table-parameter estimates and p values adjusted for age, gender and BMI). Additional joints commonly affected by OA, such as the shoulders, carpometacarpal joints, and metatarsophalangeal joints were frequently also infiltrated with activated macrophages (26%, 28%, and 14% of scans positive, respectively); 99mTc-EC20 uptake at the ankles and first metatarsophalangeal joints was strongly associated with joint pain at these sites.
Conclusions: This study provides the first direct in vivo evidence for macrophage involvement in OA and demonstrates the ability of the FolateScan technology to differentiate inflammatory and non-inflammatory activity states of OA patients. These results suggest that drugs targeting macrophages and macrophage associated inflammatory pathways may decrease OA symptoms and progression of joint structural deterioration.
Acknowledgments
This was an Investigator Initiated Study sponsored in part by Lilly USA, LLC with additional support from the Claude D Pepper OAIC P30 AG028716 and P01 AR050245. Etarfolatide was kindly donated by Endocyte.

Table-Association of 99mTc-EC20 uptake indicative of activated macrophages with severity of knee OA.

	JSN	OST	Symptoms
Site of Macrophages	parameter estimate (p value)	parameter estimate (p value)	parameter estimate (p value)
Synovium	0.157 (0.006)	0.756 (0.011)	0.231 (<0.0001)
Joint Capsule	0.234 (0.007)	0.988 (0.001)	0.231 (0.004)

68
TRANSCRIPTOMICS ON SYNOVIAL SPECIMEN OF EARLY HUMAN (CHECK) AND EXPERIMENTAL OA TO IDENTIFY PATHWAYS AND PROCESSES ASSOCIATED WITH CARTILAGE DAMAGE

A.B. Blom [†], P.L. van Lent [†], M.H. van den Bosch [†], H. Cats [‡], F. van den Hoogen [‡], P.M. van der Kraan [†], W.B. van den Berg [†]. [†] *Radboud Univ. Med. Ctr. Nijmegen, Nijmegen, Netherlands;* [‡] *Sint Maartenskliniek, Nijmegen, Netherlands*

Purpose: The majority of osteoarthritis (OA) patients show synovial inflammation, even relatively early during the disease. How synovitis contributes to the irreversible joint pathology is not known. In the present study we used microarray analysis of synovial tissue of early OA patients and of experimental OA, to identify common pathways that determine cartilage damage in this disease.
Methods: Longitudinal expression analysis was performed on murine synovial tissue at day 7, day 21 and day 42 in collagenase induced OA (CIOA) and the surgically induced DMM model (destabilization of the medial meniscus). CIOA was induced by intra-articular injection of collagenase, which causes joint instability. From a subpopulation of patients (n= 25) that entered the CHECK Cohort study (Cohort Hip and Cohort Knee) and 7 controls, synovial biopsies were collected at year 0, 2 and 5. CHECK is a prospective 10-year follow-up study on participants with early osteoarthritis-related complaints initiated by the Dutch Arthritis Association. Kellgren&Lawrence-score (KL) at inclusion was determined (n=18) and follow up measurements were performed at 2 and 5 years. Affymetrix was used for microarray, and pathway analysis was done using DAVID.